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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,016	03/05/2001	Dean K. Pettit	3253	5188

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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,016	PETTIT ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-13 and 16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-13 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7, 9-13 and 16-24 are pending and under consideration. No claim has been amended.

Rejections Over Prior Art

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9 and 16-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of U.S. Patent Number 5,217,954 (Foster et al.) and U.S. Patent Number 6,620,784 (Ferrara et al.), and in the case of claims 4-8, further in view of U.S. Patent Number 5,545,536 (Kaushansky et al.) for reasons of record in the Office Action mailed 2/23/2005. Applicants arguments filed 8/15/05 have been fully considered but are not deemed persuasive.

At page 7 of the response, applicants argue that there is no motivation to use EDTA to stabilize GM-CSF, and that references in which EDTA is used to stabilize VEGF-E and bFGF are insufficient to support the "unduly broad generalization" that it is known to use EDTA to stabilize preparations of cytokines. This argument has been fully considered but is not deemed persuasive because the motivation to use EDTA in the composition is provided by Ferrara et al.

and Foster et al., the latter especially having taught that EDTA stabilizes proteins against oxidation of free cysteine residues or metal-induced aggregation." It was well known in the art at the time the invention was made that human GM-CSF has five cysteine residues, four in the mature protein. This alone would have provided sufficient motivation to use EDTA to stabilize GM-CSF with a reasonable expectation that the resulting composition would be at least as stable as a similar composition lacking EDTA, and quite possibly more stable.

Applicants also argue that there is not sufficient disclosure in Ferrara et al. to show that EDTA actually stabilizes VEGF-E, as EDTA "is only listed as a chelating agent with many other carriers, excipients or stabilizers." This argument has been fully considered but is not deemed persuasive because it is misplaced. Ferrara et al. state that EDTA is a chelating agent known to be used in stabilizing compositions comprising VEGF-E. It is not particularly relevant *what* protein is being stabilized; that is, EDTA is added to guard against the protein of interest being oxidized, aggregated by metals, or digested by metalloproteases (which require metal ions to be active, which metal ions would be chelated by the EDTA) regardless of the identity of the protein of interest. Ferrara et al. were chosen by the examiner to demonstrate this point, as VEGF-E is a cytokine that is, like GM-CSF administered to humans, and is administered by similar means as GM-CSF. For this reason, applicants further argument at page 7 regarding the percentage sequence similarity between GM-CSF and VEGF-E is not relevant. The relevant similarities between the two proteins are that they are both cytokines that are known to be administered pharmaceutically, they both comprise cysteine residues (see SEQ ID NO: 2 of Ferrara et al.), and because they both have pharmaceutical utility, that it would be desirable to make them as stable as possible in solution, using agents known to be compatible with pharmaceutical use. Applicants implicit argument that one would not be motivated to use EDTA in a composition of a protein that does not comprise unpaired cysteine residues is not supported by fact or evidence, nor is the Examiner aware of such in the art.

Applicants argument at page 9 of the response has been fully considered, and is persuasive in that it evidences that formulation of protein pharmaceutical compositions with stabilizers such as EDTA is considered to be *routine experimentation* by the art. It remains as stated in the previous Office Action, that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to have modified the sargramostim preparation

disclosed in the LEUKINE® insert by the addition of EDTA, as taught by both Ferrara et al. and Foster et al. One of ordinary skill in the art would have been motivated to make the addition in order to prevent oxidation of the GM-CSF protein, and would have been motivated to do so in view of the recognition in the art that EDTA is generally useful for such in compositions comprising cytokines, as evidenced by Ferrara and Foster. The specific concentration of EDTA to be added would be easily determinable, and is considered well within the purview of routine experimentation by the ordinary pharmacologist, and as further evidenced by applicants arguments at page 9 of the response filed 8/15/2005. It further would have been obvious to use TRIS as a buffering agent, as it is notoriously old and well known in the art as such, for example see Kaushansky. Accordingly, the invention, taken as a whole, remains *prima face* obvious over the prior art. Further, as EDTA and benzyl alcohol were known to work by different mechanisms (the former directly preventing oxidation of proteins and therefore directly stabilizing them, the latter preventing microbial growth), it would be expected that a GM-CSF composition comprising EDTA would be at least as, and possible more stable than one without. It is noted that the cited references are but two from a broad literature comprising pharmaceutical compositions of many and varied proteins, and that it was well known in the art to combine EDTA and benzyl alcohol in compositions; the Examiner has previously cited U.S. Patent Number 5,902,785 as further evidence of such.

Finally, it remains that the results at page 13 therein are not considered to be "unexpected", as the person of ordinary skill in the art reading the above-cited references would have expected GM-CSF stored in the presence of EDTA to more stable than that without. It would appear that the results therein merely compare the presence to the absence of EDTA, and do not compare the preparations containing EDTA to comparable prior-art preparations lacking EDTA. Thus, applicants continuing arguments that the claimed composition is somehow unexpectedly more stable than that of the prior art is not supported by fact or evidence.

It remains that the claimed invention differs from the prior art solely by addition of EDTA. EDTA was a well known stabilizing agent in the art of pharmaceutical compositions comprising proteins, including cytokines, as evidenced by the above references. The person of ordinary skill in the art would have expected a composition comprising EDTA to provide a result at least as good as that of the commercially available preparation. Applicants have presented no

fact or evidence to the contrary. Accordingly, the *prima facie* finding of obviousness is maintained.

Claims 10-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of U.S. Patent Number 6,620,784 (Ferrara et al.) , and U.S. Patent Number 5,217,954 (Foster et al.), as cited in the rejection of claims 1-7, 9 and 16-24 above, and further in view of U.S. Patent Number 6,500,418 B1 (Dieckgraefe et al.) for reasons of record in the previous Office Action. Applicants arguments filed 8/15/2005 have been fully considered but are not deemed persuasive for reasons cited above.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner

10/26/2005